

Amendments to the Specification:

Please amend the title as follows:

--NOVEL ACTIN-RELATED CYTOSKELETAL ACTIN-
ASSOCIATED CYTOSEKELTON PROTEIN "LACS"--

Please amend the paragraph on page 1, line 31 through page 2, line 4, beginning, "L-NAME (N^G-Nitro-L-arginine methyl ester, hydrochloride) is a widely used NO..." as follows:

--L-NAME (N^G-Nitro-L-arginine methyl ester, hydrochloride) is a widely used NO synthase inhibitor that inhibits cNOS and iNOS. Continuous administration of L-NAME to rats can produce rats with inhibited NO production. In such model rats, increase of blood pressure as well as cardiovascular inflammatory and proliferative changes (infiltration of monocytes/macrophages, increase of MCP-1, elevation of NF-κB activity, etc.) occur within one week of L-NAME administration, and cardiovascular remodeling is observed from the fourth week onwards. Eventually, the rats die due to cardiac failure, renal failure, cerebral infarction, or such. Inflammatory and proliferative changes and arteriosclerotic lesions (pathologic changes) in rats with inhibited NO production are known to disappear when the effects of angiotensin II (AngII) or MCP-1 are suppressed.--

Please amend the paragraph on page 2, line 32 through page 3, line 4, beginning, "The present inventors have reported that NO-mediated changes in cardiovascular..." as follows:

--The present inventors have reported that NO-mediated changes in cardiovascular remodeling can occur due to a local increase of angiotensin convertase (ACE) activity in cardiac tissues, and can be suppressed almost completely by ACE inhibitors and angiotensin II receptor (AT1R) antagonists. However, many facts still remain unclear such as the mechanism of local activation of the renin-angiotensin system (RAS), the mechanism involved in the

changes of cardiovascular architecture following signaling, etc. Thus, identification of genes that play important roles in the development of cardiovascular lesions (pathologic changes) is desired. Such genes and proteins encoded by these genes are also considered to be important in terms of the prevention and treatment of cardiac diseases.--

Please amend the paragraph on page 5, line 26 through page 6, line 4, beginning, "Furthermore, the proteins of this invention are proteins comprising a polypeptide..." as follows:

--Furthermore, the proteins of this invention are proteins comprising a polypeptide encoded by a polynucleotide that hybridizes under stringent conditions with a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 2. Such proteins can be obtained by, for example, preparing probes based on the nucleotide sequence of SEQ ID NO: 2, screening a mammalian cDNA library, genomic library, and such by the hybridization method (ed. Ausubel *et al.*, Current Protocols in Molecular Biology, publish. John Wiley & Sons, section 6.3-6.4 (1987)), and expressing the obtained polynucleotides. However, the phrase "polynucleotide that hybridizes under stringent conditions with the polynucleotide comprising the nucleotide sequence of SEQ ID NO: 2" as used in this invention is not intended to restrict ~~the method for producing such~~ polynucleotides to those obtained by the hybridization method. Therefore, polynucleotides that can be produced by techniques such as the aforementioned site-directed mutagenesis are included in the definition, as long as they hybridize under stringent conditions with the nucleotide sequence of SEQ ID NO: 2. Herein, the term "stringent conditions" refers to conditions of low salt concentration or high temperature in the washing step, and includes conditions of 1x SSC, 0.1% SDS, 37°C (or 55°C).--

Please amend the paragraph on page 14, lines 12 through 29, beginning, "In the present invention, the LACS protein was shown to bind to actin..." as follows:

--In the present invention, the LACS protein was shown to bind to actin. By regulating ~~inhibiting~~ the binding between the LACS protein and actin, actin polymerization may be enhanced or suppressed. Therefore, compounds that inhibit the binding between the LACS protein and actin may be candidates of pharmaceuticals for cardiovascular diseases. Methods for screening compounds that inhibit the binding of the LACS protein can be performed using the binding between the protein and actin as an index. More specifically, such compounds can be screened, for example, by the steps of:

- (1) contacting a test compound with a protein of this invention or a partial peptide thereof in the presence of actin;
- (2) detecting the binding of actin to the protein or partial peptide; and
- (3) selecting a test compound that suppresses or inhibits the binding of actin to the protein or partial peptide.

The partial peptides used here must comprise the portion(s) involved in the binding between the LACS protein and actin. Such partial peptides can be obtained easily by analyzing the actin affinity of the various fragments produced upon digestion of the LACS protein. Furthermore, binding between the LACS protein and actin may be carried out by methods as described in Example 7, using LACS antibodies and actin antibodies, but is not limited thereto.--

Please amend the heading for "Example 1" on page 16, line 19 as follows:

--[Example 1] Gene isolation by Suppression Subtractive Hybridization (SSH)--

Please amend the paragraph on page 17, lines 2 through 15, beginning, "A cDNA library was constructed, and a full-length cDNA encoding LACS was..." as follows:

--A cDNA library was constructed, and a full-length cDNA encoding LACS was isolated by screening. More specifically, poly (A)⁺ RNAs obtained from WKY rats on the first day of L-NAME administration were used to construct a λ ZAPII cDNA library using random primers. Next, by repeated screening using the LACS gene fragments as probes, an approximately 12-kb

cDNA in full length was obtained as the LACS gene. Sequencing of this cDNA was performed using the ABI PRISM310 DNA Sequencer (ABI/ Perkin Elmer). The obtained nucleotide sequence is shown in SEQ ID NO: 1. Characteristic sequences such as signal sequences or transmembrane regions could not be found in the amino acid sequence (SEQ ID NO: 2) predicted from the nucleotide sequence. Therefore, it was difficult to predict the properties and functions of LACS from the sequence alone. However, a proline-rich sequence exists at the C terminus of the predicted amino acid sequence, suggesting an SH3-binding domain homology. SH3 is a homologous portion of approximately 70 amino acids seen in the Src kinase family. The SH3-binding domain is a proline-rich sequence of approximately ten amino acids.--

Please cancel the present "SEQUENCE LISTING", pages 1/93-93/93, and insert therefor the accompanying paper copy of the Substitute Sequence Listing, page numbers 1 to 12, at the end of the application.